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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/460,186	06/02/95	VON BORSTEL	R 1331-138

KUNZ, G — EXAMINER

12M1/0903

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ART UNIT	PAPER NUMBER
1211	5

DATE MAILED: 09/03/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6-2-95.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

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– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-410-238/40050

The Group and/or Art Unit location of your application in the PLO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1211.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper tames extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 - 25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 - 36 of copending application Serial No. 08/472,210; claims 48 - 74 of copending application Serial No. 08/473,332; claims 1 - 36 of copending application Serial No. 08/472,210; claims 75 - 87 of copending application Serial No. 08/176,485; and claims 30 - 35 of copending application Serial No. 08/465,455. Although the conflicting claims are not identical, they are not patentably distinct from each other because all of the claims are directed to reducing the toxicity of a pyrimidine nucleoside analogue chemotherapeutic agent comprising the coadministration of acylated U, acylated dU, acylated C, or acylated dC. Whether the nucleoside analogue is used as an anticancer agent or an antiviral agent, the invention is basically the same. In fact, some chemotherpeutic agent are both anticancer and antiviral drugs.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 - 15, 18 - 19, and 22 - 25 are rejected under 35 U.S.C. § 103 as being unpatentable over Martin et al. (Cancer Res., 1982) or Sommadossi et al. (Antimicrobial Agents and Chemotherapy, 1988) view of Von Borstel et al. (WO 89/03837) and Falcone et al. (Blood, 1990).

The claims are directed to a method for treating cancer comprising administering a pyrimidine nucleoside analog and acylated uridine, deoxyuridine, cytidine or deoxycytidine. Claims 18 and 19 include a uridine phosphorylase as an additional component.

Martin et al. teaches that administering exogenous uridine can reduce the toxicity of 5-FU and actually "rescue" mice from a toxic dose of 5-FU. Sommadossi et al. also teaches

that uridine administration can reduce the toxicity of a pyrimidine nucleoside analog, AZT. Neither Martin et al. nor Sommadossi et al. teaches the use of acylated uridine or cytidine.

However, Von Borstel et al. discloses a method for elevating the serum and tissue levels of free uridine or cytidine comprising administering the acylated prodrugs thereof (see claims 10 - 15). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated uridine or cytidine as taught by Von Borstel et al. in place of the free uridine taught by Martin et al. and Sommadossi et al. in order to increase the serum and tissue levels of uridine and therefore, reduce the toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of said nucleoside analog. Thus, the invention is prima facie obvious in the absence of clear and convincing evidence to the contrary.

Neither Martin or Sommadossi nor Von Borstel teaches the use of an inhibitor of uridine nucleoside phosphorylase as a way to increase serum and tissue levels of free uridine. However, Falcone et al. does teach the use of an inhibitor of uridine nucleoside phosphorylase, benzylacyclouridine, to increase the serum and tissue levels of free uridine, and thereby reducing the toxicity of AZT. Therefore, a method of using either acylated U

or C in combination with a uridine phosphorylase inhibitor would also have been obvious to the person or ordinary skill in the art at the time of the invention wanting to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

Claims 16 - 17 and 20 - 21 are rejected under 35 U.S.C. § 103 as being unpatentable over Bhalla et al. (Blood, 1987) in view of Von Borstel et al. (WO 89/03838) and Hanze et al. (4,017,606).

Claims 16 - 17 are directed to a method for preventing or treating toxicity due to pyrimidine nucleoside analogs comprising the administration of a pyrimidine nucleoside analog and an acylated deoxycytidine. Claims 20 - 21 further include a cytidine deaminase inhibitor.

Bhalla et al. teaches that the administration of deoxycytidine reduces the toxicity of cytosine arabinoside. Bhalla does not teach the use of acylated deoxycytidine in place of free deoxycytidine. However, Von Borstel et al. does teach the use of acylated deoxycytidine in place of free deoxycytidine in order to obtain higher serum and tissue levels of deoxycytidine (see claim 32). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated deoxycytidine as taught by Von Borstel et al. for deoxycytidine as taught be Bhalla et al.

for the purpose of increasing the serum and tissue levels of free deoxycytidine, thus reducing further the toxicity of cytosine arabinoside or other pyrimidine nucleoside analogs.

Neither Bhalla nor Von Borstel disclose a cytidine deaminase inhibitor. However, Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42 - 61) and its use to prevent the degradation of a cytidine nucleoside analog. Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxy-cytidine and tetrahydrouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinosie or any other pyrimidine nucleoside analog.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3 - 15, 18 - 19, and 24 - 25 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to uridine, cytidine, 2'-deoxyuridine, and 2'-deoxy-cytidine as the non-methylated pyrimidine nucleosides. The

term non-methylated pyrimidine nucleosides also includes cytosine arabinoside, 5-azacytidine, and deazacytidine. These nucleoside analogs are "non-methylated pyrimidine nucleosides" but they would not be expected to reduce the toxicity of other pyrimidine nucleoside analogs. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification and claim 11 are objected to because the word "tegafur" is not capitalized nor is there a superscription " R " to the right of this word indicating that it is a trademark.

The claims are further objected to because the position of the fluorine in fluorouridine is not indicated in each instance. "Fluorouridine" should be "5-fluorouridine". "5'-deoxyfluoro-uridine" should be written as "5'-deoxy-5-fluorouridine".

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kight, can be reached on (703) 308-0204. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Gary L. Kunz
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PRIMARY EXAMINER
GROUP 1200

Gary L. Kunz, Ph.D.
August 28, 1996